REMARKS

Claims 1, 4-9, 11, 12, 14-31 and 33-53 are pending in the present application. Claims 1, 4-9, 11, 12, 14-30, 33, and 36-53 are withdrawn from consideration. Claims 31, 34, and 35 stand rejected. Reconsideration of the above application is respectfully requested.

Rejection under 35 USC §103

The Examiner rejected claims 31, 34, and 35 under 35 USC §103 as being obvious over Harkin et al. in view of Wong et al. The Examiner alleges that Harkin et al. teaches a combination of the pharmaceutical agents reboxetine and sertraline used in a method for treating depression. The Examiner admits that Harkin et al. does not teach the S,S-entantiomer of reboxetine and further alleges that Wong et al. teaches a pharmaceutical composition of the S,S-enantiomer of reboxetine. In light of the Examiner's allegations, the Examiner concludes that ones skilled in the art "would be motivated to utilize the S,S-enantiomer of reboxetine in the composition of Harkin et al. because Wong et al. teaches that the S,S-enantiomer of reboxetine does not have the adverse side effect profile associated with the racemic mixture." Office Action, 12/01/06, page 2.

In response, applicants submit that a case of *prima facie* obviousness has not been established and respectfully request reconsideration and withdrawal of the rejection. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As an initial matter, Applicants respectfully point out that Harkin et al. does not teach, as the Examiner alleges, the combination of reboxetine and sertraline. Harkin et al. only relates to the use of reboxetine as a single agent for antidepressant activity in rats. Harkin et al. makes no reference whatsoever to the use of reboxetine in combination with sertraline to treat depression. Accordingly, based on the Examiner's own reasoning, claims 31, 34, and 35 cannot be obvious over Harkin et al. in view of Wong et al.

Assuming arguendo Harkin et al. does teach the combination of reboxetine and sertraline to treat depression, the Examiner has nonetheless failed to show where in any of the cited references there is a teaching, suggestion, or motivation to arrive at the claimed invention. Specifically, the Examiner has not shown where the motivation to combine the references comes from. The Examiner claims that "one would be motivated to utilize the S,S-enantiomer of reboxetine in the composition of Harkin et al. because Wong et al. teaches that the S,S-enantiomer of reboxetine does not have the adverse side effect profile associated with the racemic mixture." Office Action, 12-1-07, page 3.

Applicants respectfully disagree. Applicants respectfully submit that the Examiner has failed to indicate where the motivation exists in the references to combine them. The favorable side effect profile discussed in Wong et al., is recited in the context of treating depression. However the current application is directed to compositions useful for treating smoking cessation in humans. Thus, it is the Examiner's burden to specify where in the reference (by page and line number) why one skilled in the art would be motivated to combine S,S-reboxetine, which in the context of treating depression is more effective than the racemate, with sertraline for treating smoking cessation. Further, applicants respectfully submit that based on the reason recited by Wong et al. (col. 4, line 58) as the cause of side effects for reboxetine, which is that it also inhibits serotonin and dopamine in addition to norepinephrine, one skilled in the art would be motivated to instead combine racemic reboxetine with sertraline because one skilled in the art, seeking to find an improved effect, would choose two agents that have overlap with respect to the neurotransmitters they modulate, in the hope of finding synergy. Thus, applicants submit the Wong et al., in explaining the reasoning for the side effect profile of S,S-reboxetine, actually teaches away from the claimed invention.

In view of the remarks above, applicants respectfully submit that the Examiner has failed to meet their burden to show where motivation exits to arrive at the claimed invention.

Assuming arguendo there is motivation to combine the references, applicants respectfully submit there is still no reasonable expectation of success. Firstly, given that stereochemistry can have vast difference in pharmacological effect (See Wong et al., col. 4, lines 6-18), applicants respectfully submit that one skilled in the art could not predict the effect of combining S,S-reboxetine with sertraline. Wong et al. relates to S,S-reboxetine's improved side effect profile over the racemic mixture as a single agent only. Wong et al. speaks nothing to how the improved side effect profile of S,S-

reboxetine would be influenced when combined with sertraline. Applicants respectfully submit that one skilled in the art would appreciate the inherent uncertainty of how combining sertraline with S,S-reboxetine versus racemic reboxetine. This would especially be true with respect to the side effect profile of reboxetine because "it has been found that such side effects occur in part because reboxetine...is blocking serotonin..." Wong et al. col. 4, lines 55-60. Thus, one skilled in the art could not predict the effect of combining these two different agents because both modulate serotonin in the body and thus the unpredictability of how they would interact and modulate serotonin in sum is high. Furthermore, since the negative side effects of racemic reboxetine discussed in Wong et al. is attributable to reboxetine's lack of high selectivity for inhibiting norepinephrine over serotonin and dopamine (see Wong et al., col 4, lines 55-60), one skilled in the art would believe that any increased effect attributable to such a combination, would be even more enhanced by the use of racemic reboxetine over S,S-reboxetine. This is be because one skilled in the art would believe that any increase in effect from such a combination would be likely attributable the dual effect of reboxetine and sertraline on the same neurotransmitter (i.e., serotonin), serotonin is the only neurotransmitter that both agents inhibit. Since S,S-reboxetine has high selectivity for inhibiting norepinephrine only (it does not inhibit serotonin to the same degree that the racemate does), any effect would be predicted to be less.

Finally, the current application is directed to a combination of S,S-reboxetine and sertraline for promoting smoking cessation whereas Wong et al. relates to the use of reboxetine as an anti-depressant. Hence, because different a different effect is desired (anti-depression versus smoking cessation) it would not be clear to one skilled in the art that the S,S-reboxetine, with it's known side-effect profile in the context of anti-depression, would be a favorable in the context of smoking cessation since the cause of the side-effects of racemic reboxetine (the inhibition of another monoamines including norepinephrine), may very well also be the cause of what makes reboxetine in combination with sertraline an effective smoking cessation composition. Thus, one skilled in the art would actually predict that S,S-reboxetine would be less effective than racemic reboxetine when used in combination with sertraline to help promote the cessation of smoking, and not the other way around.

Based on the remarks above, applicants respectfully submit that the Examiner has failed to show that there is a reasonable expectation of success.

Finally, the cited references do not teach or suggest all the claim limitations. As discussed above, Harkin et al. only relates to the use of reboxetine as a single agent on rats for antidepressant activity and Wong et al. only relates to S,S-reboxetine.

Neither reference relates to the use of sertraline alone or in combination with reboxetine, let alone S,S-reboxetine. Hence the cited references do not teach or suggest all the claim limitations of claim 31, a pharmaceutical composition comprising S,S-reboxetine and an agent selected from nicotine, an antidepressant, an anxiolytic, a nicotinic receptor antagonist, an opioid antagonist, and mixtures thereof.

In view of the remarks above, applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorney at the telephone number provided.

No fee is believed necessary in connection with filing this Amendment. However, if any additional fee is found necessary in connection with filing this Amendment, authorization is hereby given to charge such fee to Deposit Account No. 16-1445.

A favorable response is earnestly solicited.

Respectfully submitted,

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